

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
9 October 2003 (09.10.2003)

PCT

(10) International Publication Number
WO 03/082266 A1(51) International Patent Classification⁷: **A61K 31/365**,
31/70, 31/135, 31/137, 31/352, 31/495, 31/435, 31/395,
A61P 31/12, 31/04, 31/10, 31/12, 31/18, 35/00, 31/00

(21) International Application Number: PCT/GB03/01369

(22) International Filing Date: 28 March 2003 (28.03.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
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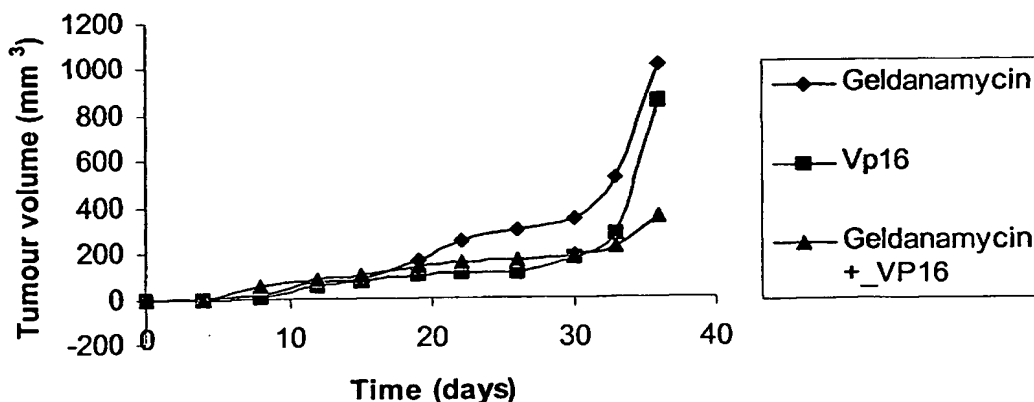
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Park Place, Leeds LS1 2RY (GB).(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: USE OF TOPOISOMERASE INHIBITORS AND HEAT SHOCK PROTEIN 90 INHIBITORS FOR USE IN CHEMOTHERAPY



(57) Abstract: The present invention relates to the use of a first agent that attenuates Topoisomerase II (Topo II) activity and a second agent that inhibits Heat Shock Protein 90 (HSP90) for use in chemotherapy. The agents are particularly useful in the treatment of cancer and destruction of micro-organisms. The invention also relates to screening methods, diagnostic methods and methods for evaluating or monitoring chemotherapy regimens.

INTERNATIONAL SEARCH REPORT

Internat Application No

PCT/60/01369

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7	A61K31/365	A61K31/70	A61K31/135	A61K31/137	A61K31/352
	A61K31/495	A61K31/435	A61K31/395	A61K31/12	A61P31/04
	A61P31/10	A61P31/12	A61P31/18	A61P35/00	A61P31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, PASCAL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	<p>BARKER CR; RACKSTRAW S; HAMLETT J; PENNINGTON SR; WATSON AJM; JENKINS JR: "Topoisomerase II associated proteins in colon cancer cells" GUT, 1 April 2003 (2003-04-01), page a56 XP009013268 page 56, right-hand column, paragraph 3 - paragraph 6</p> <p style="text-align: center;">-/-</p>	1-5, 14, 15, 30, 31

☒ Further documents are listed in the continuation of box C.☐ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

10 July 2003

Date of mailing of the international search report

05/08/2003

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INTERNATIONAL SEARCH REPORT

Internat Application No

PCT/LL 03/01369

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	MÜNSTER PN; BASSO A; SOLIT D; NORTON L; ROSEN N: "Modulation of Hsp90 Function by ansamycins sensitizes breast cancer cells to chemotherapy-induced apoptosis in an rb- and schedule-dependent manner" CLINICAL CANCER RESEARCH, vol. 7, 1 August 2001 (2001-08-01), pages 2228-2236, XP002246587 page 2233, left-hand column, paragraph 4 page 2234; figures A,B	1-3,6, 14,16
X	BLAGOSKLONNY MV; FOJO T; BHALLA KN; KIM J-S; TREPEL JB; FIGG WD; RIVERA Y; NECKERS LM: "The Hsp90 inhibitor geldanamycin selectively sensitizes Bcr-Abl-expressing leukemia cells to cytotoxic chemotherapy" LEUKEMIA, vol. 15, 2001, pages 1537-1543, XP001118520 page 1540, right-hand column	1-3,6, 14,15
P,X	BLAGOSKLONNY MV: "Hsp-90-associated oncoproteins: multiple targets of geldanamycin and its analogs" LEUKEMIA, vol. 16, April 2002 (2002-04), pages 455-462, XP009013263 page 458, right-hand column, paragraph 6 page 458, left-hand column, paragraphs 2,3	1-3,6, 14,15
X	NECKERS L: "HSP90 inhibitors as novel cancer chemotherapeutic agents" TRENDS IN MOLECULAR MEDICINE, vol. 8, no. 4, 2002, pages 55-61, XP002246588 page 58, right-hand column, paragraph 4	1-3,6, 14,16

INTERNATIONAL SEARCH REPORT

Inter Application No.
PCT/ISA/210 03/01369

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claim 1 relates to a use of compounds for chemotherapy which are defined by reference to a desirable characteristic or property, namely

- "agent that attenuates Topoisomerase II" and "agent that inhibits Heat Shock Protein 90"

Claims 1,2, 14-25 cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT only for a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. The terms "agent that attenuates Topoisomerase II" and "agent that inhibits Heat Shock Protein 90" are open-ended as they may relate to a large number of possible compounds able to be "agents which attenuate Topoisomerase II" and "agents, which inhibit Heat Shock Protein 90". Therefore the terms "agent that attenuates Topoisomerase II" and "agent that inhibits Heat Shock Protein 90" was searched as "agents, which attenuate Topoisomerase II" and "agents, which inhibit Heat Shock Protein 90", but so far not identified as such. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds specified on pages 8-18 of the description.

Furthermore, the skilled person is unable to determine unambiguously which regimens fall under the scope of the expression:

- "chemotherapy" in claims 1-17, 26-33

(Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the diseases in claims 18-25).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.